Apathy Following Cerebrovascular Lesions

Sergio E. Starkstein, MD, PhD; J. Paul Fedoroff, MD; Thomas R. Price, MD; Ramón Leiguarda, MD; Robert G. Robinson, MD

Background and Purpose: Although apathy has been reported to constitute a frequent sequela of stroke lesions, there have been no prospective studies on the frequency and correlates of apathy after stroke lesions. In the present study, we examined the frequency and correlates of apathy in a consecutive series of 80 patients with cerebrovascular lesions.

Methods: We included patients within the first 10 days after a stroke lesion. Patients were examined with a comprehensive neuropsychiatric battery that included the Apathy Scale.

Results: Eighteen patients (22.5%) showed apathy, nine of whom were also depressed. On the other hand, 18 patients (22.5%) showed depression in the absence of apathy. Although depression and apathy may exist independent of one another, major depression (but not minor depression) was associated with an increased frequency of apathy. Apathy was also significantly associated with older age, cognitive impairments, and deficits in activities of daily living. Finally, apathy was significantly associated with lesions in the posterior limb of the internal capsule.

Conclusions: These findings demonstrate that apathy is a frequent finding among patients with acute stroke lesions and may coexist with important emotional and cognitive poststroke disturbances. (Stroke. 1993;24:1625-1630.)

Key Words • cerebrovascular disorders • depression • emotions

Apathy is defined as the absence or lack of feeling, emotion, interest, or concern. Although no formal studies on the frequency and correlates of apathy have been performed in patients with stroke lesions, this condition has been frequently recognized among stroke victims. For instance, Helgason et al reported apathy as one of the primary clinical features in their series of patients with stroke lesions in the anterior choroidal artery territory.

In this study, we have systematically examined the presence and severity of apathy in a consecutive series of patients with cerebrovascular lesions. We used a standardized scale to measure the severity of apathy and demonstrated its reliability and validity. Here we report on the frequency as well as demographic, clinical, and neuroradiological correlates of apathy in patients with stroke lesions.

Subjects and Methods

Subjects

Subjects included in this study were selected from 96 consecutive admissions to the University of Maryland Hospital, Baltimore, for treatment of acute thrombembolic infarction or intracerebral hemorrhage. Patients with a prior history of cerebrovascular lesions (n=10) or moderate to severe comprehension deficits on the short form of the Token Test (n=6) were excluded from the study. However, patients with nonfluent aphasia who could reliably answer questions with affirmative or negative answers were included.

Neurological Examination

The neurological examination was performed and a diagnosis made using the criteria established by the Stroke Data Bank of the National Institute of Neurological Disorders and Stroke, Bethesda, Md. Motor deficits were scored as mild (slight weakness or movement against resistance), moderate (movement against gravity), or severe (movements without gravity or no movements). Sensory deficits were assessed with the pin test and were scored as present or absent. Language disturbances were classified into the following categories: Broca, Wernicke, global, and anoma. Dysarthria was rated as present or absent. All neurological evaluations were done by a neurologist (T.R.P.) who was blind to findings on the psychopathological and neuropsychological examination.

Psychiatric Examination

After giving informed consent, patients were administered a series of standardized quantitative measures of mood, cognitive function, and physical impairment. We previously showed that these instruments give reliable and valid measurements in this stroke population.

The modified Present State Examination (PSE), a structured psychiatric interview that elicits symptoms related to depression and anxiety, was administered by

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a psychiatrist. With the use of the symptoms elicited by the PSE, a diagnosis of major depression was made using the symptom criteria of the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III).8 The method for conversion of PSE symptoms to DSM-III diagnostic criteria and their concurrence with Research Diagnostic Criteria was demonstrated in a previous publication.9

The Hamilton Rating Scale for Depression,9 a 17-item interviewer-rated scale, was used to measure psychological and autonomic symptoms of depression. The Hamilton Rating Scale for Anxiety,10 a 14-item interviewer-rated scale, was used to measure the severity of generalized or persistent anxiety.

The Mini-Mental State Examination (MMSE)11 and the Johns Hopkins Functioning Inventory (JHFI)12 were also administered to each patient. The MMSE has been shown to be reliable and valid in assessing a limited range of cognitive functions in patients with stroke. Scores range from 0 to 30, and a score of 23 or below indicates significant cognitive impairment. The JHFI contains 10 items and evaluates the degree of independence in activities of daily living. Scores range from 0 to 27, and higher scores indicate greater degree of impairment. In conjunction with the psychiatric evaluation, quantitative assessments of available social supports were made using the Social Ties Checklist.13

Apathy was measured using the Apathy Scale (AS), which is an abridged version of Marin’s Apathy Scale.14 The AS is administered by the examiner, and scores range from 0 to 42 (higher scores indicate more severe apathy). A comprehensive description of the AS is provided elsewhere.15 Normal subjects were reported to score (mean±SD) 3.2±3.6, and 95% of them scored below 9 points.15

The neuropsychiatric evaluations were carried out by a psychiatrist (J.P.F.) blind to the rest of the neurological, neuroradiological, and neuropsychological data.

Computed Tomographic Scan Examination

Computed tomographic (CT) scans were obtained from all patients included in the study and were read blind to clinical findings. All CT scans were performed using a General Electric 9900 scanner, and 5-mm-thick slices were obtained parallel to the canthomeatal line.

The damaged area was localized in specific brain regions according to the procedure of Levine and Grek.16 Lesion volume (expressed as a percentage of total brain volume) was calculated from the ratio of the largest cross-sectional area of the lesion to the area of the brain slice that included the body of the lateral ventricles. We have previously demonstrated the reliability of this procedure and its high correlation with other methods of determining lesion volume.17

Statistical Analysis

Statistical analysis was performed using means and standard deviations, one- and two-way analysis of variance (ANOVA) with planned comparisons, and t tests. Frequency distributions were analyzed using contingency tables and \( \chi^2 \) tests, with Yates’ correction for expected cell sizes less than 10. All probability values are two-tailed.

Results

Demographic Findings

A frequency distribution of AS scores for all 80 patients showed a bimodal distribution, and a cutoff score of 14 points separated both modes. Validity was examined by asking a neurologist (S.E.S.) who was blind to the AS scores to rate 12 consecutive patients as apathetic or nonapathetic. All ratings were determined after a comprehensive neurological evaluation. Six patients were rated as apathetic and the remaining six as nonapathetic. Apathetic patients had significantly higher AS scores than nonapathetic patients (apathetic score [mean±SD], 14.8±5.7; nonapathetic, 5.5±2.2; \( t=3.70, df=10, P<.001 \)). Using a cutoff score of 14 points or more for apathy, the sensitivity of the scale was 66%, and the specificity was 100%. The interrater reliability of the AS, examined in 10 consecutive patients rated during a single interview, was very high (\( r=.96, df=8, P<.01 \)).

A two-way ANOVA for age (factor 1, apathy; factor 2, depression) showed a significant effect for apathy (patients with apathy [with or without depression] were significantly older than patients without apathy) (Table 1). Depressed patients had a significantly higher frequency of personal history of psychiatric disorders. No

### Table 1. Demographic Findings in 80 Patients With Cerebrovascular Lesions

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Depressed</th>
<th>Apathetic</th>
<th>Apathetic+Depressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>44</td>
<td>18</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Age, mean±SD y*</td>
<td>61.1±12.9</td>
<td>51.0±15.7</td>
<td>64.0±12.4</td>
<td>63.8±12.6</td>
</tr>
<tr>
<td>Education, mean±SD y</td>
<td>9.5±3.1</td>
<td>9.9±2.9</td>
<td>11.0±2.7</td>
<td>9.8±4.5</td>
</tr>
<tr>
<td>Race, % black</td>
<td>66</td>
<td>66</td>
<td>78</td>
<td>33</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>39</td>
<td>55</td>
<td>44</td>
<td>67</td>
</tr>
<tr>
<td>Alcoholism, % positive</td>
<td>14</td>
<td>6</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>Personal hx of psychiatric disorder, % positive†</td>
<td>16</td>
<td>33</td>
<td>11</td>
<td>56</td>
</tr>
<tr>
<td>Family hx of psychiatric disorder, % positive</td>
<td>20</td>
<td>17</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Handedness, % right-handers</td>
<td>90</td>
<td>94</td>
<td>89</td>
<td>75</td>
</tr>
<tr>
<td>Time since stroke, mean±SD d</td>
<td>6.1±3.8</td>
<td>5.9±4.1</td>
<td>6.9±4.7</td>
<td>6.6±4.2</td>
</tr>
</tbody>
</table>

* \( F_{1,78}=3.96, P<.05 \)

† \( \chi^2 = 8.2, df=3, P<.05 \)
significant between-group differences were found on the remaining demographic variables.

**Neurological Findings**

No significant between-group differences were observed on motor, sensory, visual, and language disturbances (Table 2).

**Psychiatric Findings**

Based on DSM-III criteria, patients were also classified as (major or minor) depressed or nondepressed. Nine of the 80 patients (11.25%) showed apathy in the absence of depression, 9 patients (11.25%) had both apathy and depression, 18 patients (22.5%) had depression but no apathy, and the remaining 44 patients (55%) had neither apathy nor depression. A hypothesis of increased frequency of apathy based on the existence of depression was not statistically substantiated ($\chi^2=2.74$, $df=1$, $P=NS$). Thus, the overall group of depressed patients were no more likely to have apathy than nondepressed patients.

In the depression-only group, 10 patients (56%) had minor depression, and 8 patients (44%) had major depression. In the apathy+depression group, 2 patients (22%) had minor depression, and 7 patients (78%) had major depression. A hypothesis of increased frequency of apathy based on the presence of major depression was statistically substantiated ($\chi^2=5.73$, $df=1$, $P<.02$) (Table 3). Moreover, a one-way ANOVA for apathy scores between major depressed, minor depressed, and nondepressed patients showed that major depressed patients had significantly higher scores than either minor depressed or nondepressed patients ($F=4.44$, $df=2.78$, $P=.01$; major versus minor depression, $P=.009$; major versus no depression, $P= .009$). On the other hand, no significant differences were found between minor depressed and nondepressed patients. These findings indicate that although major depression and apathy can also occur independently, apathy is significantly associated with major but not minor depression.

As expected, there was a significant effect for depression on depression scores (PSE and Hamilton Depression Scale) (ie, depressed patients had significantly higher depression scores) and for apathy on apathy scores (apathetic patients showed significantly higher apathy scores) (Table 3).

There was a significant effect for depression on anxiety scores (depressed patients had significantly higher anxiety scores than nondepressed patients).

There was a significant effect for apathy on MMSE scores (patients with apathy had significantly more severe cognitive impairments), as well as a significant effect for apathy and depression on JHFI scores (activ-

### Table 2. Neurological Findings in 80 Patients With Cerebrovascular Lesions

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=44)</th>
<th>Depressed (n=18)</th>
<th>Apathetic (n=9)</th>
<th>Apathetic+Depressed (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor deficits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>27 (12)</td>
<td>33 (6)</td>
<td>33 (3)</td>
<td>11 (1)</td>
</tr>
<tr>
<td>Moderate</td>
<td>7 (3)</td>
<td>11 (2)</td>
<td>22 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Severe</td>
<td>23 (10)</td>
<td>17 (3)</td>
<td>22 (2)</td>
<td>56 (5)</td>
</tr>
<tr>
<td><strong>Sensory deficits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aphasia</td>
<td>39 (17)</td>
<td>28 (5)</td>
<td>56 (5)</td>
<td>33 (3)</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>43 (19)</td>
<td>44 (8)</td>
<td>33 (3)</td>
<td>33 (3)</td>
</tr>
</tbody>
</table>

Values are percent positive, with number of patients in parentheses.

### Table 3. Psychiatric Findings in 80 Patients With Cerebrovascular Lesions

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Depressed</th>
<th>Apathetic</th>
<th>Apathetic+Depressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present State Exam*</td>
<td>2.1 ±3.0</td>
<td>21.1 ±12.2</td>
<td>7.2 ±8.0</td>
<td>26.6 ±7.4</td>
</tr>
<tr>
<td>Hamilton Depression</td>
<td>1.0 (2.0)</td>
<td>13.1 (9.2)</td>
<td>3.1 (3.9)</td>
<td>14.2 (7.8)</td>
</tr>
<tr>
<td>Hamilton Anxiety</td>
<td>1.1 (2.2)</td>
<td>12.4 (11.0)</td>
<td>2.3 (3.3)</td>
<td>7.5 (6.6)</td>
</tr>
<tr>
<td>Major depression, %</td>
<td>0</td>
<td>44</td>
<td>0</td>
<td>78</td>
</tr>
<tr>
<td>Minor depression, %</td>
<td>0</td>
<td>56</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>Apathy Scale§</td>
<td>8.9 (4.1)</td>
<td>8.2 (3.2)</td>
<td>21.7 (4.9)</td>
<td>23.1 (5.7)</td>
</tr>
<tr>
<td>Mini-Mental State</td>
<td>23.5 (6.3)</td>
<td>24.6 (4.8)</td>
<td>20.1 (7.1)</td>
<td>14.4 (8.0)</td>
</tr>
<tr>
<td>Johns Hopkins Functioning Inventory</td>
<td>4.8 (4.0)</td>
<td>6.2 (3.9)</td>
<td>7.6 (5.8)</td>
<td>13.7 (5.5)</td>
</tr>
<tr>
<td>Social Ties Checklist</td>
<td>2.9 (2.4)</td>
<td>3.2 (1.4)</td>
<td>3.8 (1.7)</td>
<td>3.8 (2.6)</td>
</tr>
</tbody>
</table>

Values are mean±SD scores unless otherwise indicated.

*Depression, $F_{(1,79)}=48.1$, $P<.0001$.
†Depression, $F_{(1,79)}=59.2$, $P<.0001$.
‡Depression, $F_{(1,79)}=23.2$, $P<.0001$; Depression x Apathy, $F_{(1,79)}=3.13$, $P=.08$.
§Apathy, $F_{(1,79)}=140.1$, $P<.0001$.
|APathy, $F_{(1,79)}=11.5$, $P<.001$; Apathy x Depression, $F_{(1,79)}=2.85$, $P=.09$.
|Apathy, $F_{(1,79)}=18.4$, $P<.0001$; Depression, $F_{(1,79)}=9.6$, $P=.002$; Apathy x Depression, $F_{(1,79)}=3.72$, $P=.05$. |
ities of daily living) (apathetic and/or depressed patients had significantly more impairments in activities of daily living). A significant apathy×depression interaction demonstrated that the apathetic+depressed group had the most severe impairments in activities of daily living (Table 3).

Finally, no significant between-group differences were found on Social Ties scores.

**Neuroradiological Findings**

There were no significant between-group differences in lesion size and side (Table 4). However, patients with apathy only had a significantly higher frequency of lesions involving the posterior limb of the internal capsule than the other three groups (Table 4). No other significant between-group difference in lesion location was found.

**Discussion**

This is the first empirical study of apathy in stroke patients, and it showed several important findings. First, while apathy was a frequent finding among stroke patients (23% of a consecutive series of stroke patients had apathy), half of them were also depressed. Second, apathetic patients were significantly older than nonapathetic patients. Third, apathy was significantly associated with major but not minor depression. Fourth, patients with apathy had significantly more severe cognitive impairments and deficits in activities of daily living than nonapathetic patients. Finally, apathy was significantly associated with lesions involving the posterior limb of the internal capsule.

Before further discussion, some limitations of our study should be pointed out. First, the group with pure apathy and positive CT scans was rather small, and the present neuroradiological findings should be considered preliminary. Second, although overall depression was not more frequent in the apathetic than nonapathetic groups, apathetic patients had a significantly higher frequency of major depression. Thus, it might be argued that defining apathy by a cutoff score led to mixing less severe apathy, which may be based on “depressive symptoms,” with depression, therefore creating a false association. Although this is a possibility, one might expect that compared with nondepressed patients, minor depression would also be associated with apathy. Apathy, however, was just as common among nondepressed as minor depressed patients. Future studies may examine whether there are differences between patients with apathy and major depression and patients with apathy and minor depression. Finally, finding a significant association between apathy and lesions in the posterior limb of the internal capsule may be due to a type 1 statistical error, since multiple comparisons for lesion location were carried out. However, this finding is not surprising since the association between posterior internal capsule lesions and apathy has been previously reported. This issue, however, will need further studies with larger series of patients.

The first important finding was the relatively high frequency of apathy in stroke, since about one quarter of our sample was apathetic. It should be stressed that even nonapathetic stroke patients had higher scores than the mean for normal control subjects, supporting the contention of Adams and Victor that apathy is a frequent psychosocial alteration in patients with cerebral disease.

Similar to our previous finding in patients with poststroke depression, poststroke apathy was significantly associated with cognitive impairments and deficits in activities of daily living. However, whether apathy may cause cognitive impairments or vice versa cannot be determined with the present study design.

Another important finding was the significant association between apathy and major but not minor depression. We have previously reported that among stroke patients, major and minor depression have different correlates. For instance, patients with major (but not minor) depression have an increased frequency of lesions of the left frontal cortex and head of the caudate.
major depression spontaneously remits 1 to 2 years after the stroke, while minor depression usually lasts 2 or more years\textsuperscript{21}; and major but not minor depression is associated with a significant cognitive impairment\textsuperscript{22} and a failure to suppress serum cortisol after dexamethasone administration.\textsuperscript{23,24}

The present finding that apathetic patients were more likely to have major depression than patients without apathy suggests that major depression and apathy may be causative of one another or may share similar mechanisms. Alternatively, the fact that both psychomotor retardation and markedly diminished interest in daily activities (two important symptoms of apathy) are included in the diagnostic criteria for major (but not dysthymic) depression may account for the significant association between apathy and major depression. We have previously hypothesized that poststroke major depression is secondary to disruption of subcortical-basal ganglia neural pathways,\textsuperscript{18} and we demonstrated cortical serotoninergic deficits in patients with poststroke major depression.\textsuperscript{25} Apathy has been frequently described in neurological disorders that are secondary to biogenic amine abnormalities such as Parkinson's disease, where a significant association between "cognitive slowness" and catecholaminergic levels in cerebrospinal fluid has been reported.\textsuperscript{26} The fact that nigrostriatal dopamine levels show a significant reduction with age may underlie our present finding of significantly more apathy in elderly patients.\textsuperscript{27}

Our finding that some patients showed apathy in the absence of major depression suggests that the production of apathy may result from a different mechanism. The higher frequency of lesions involving the posterior limb of the internal capsule in poststroke apathetic patients in the present study replicates the finding of Helgason et al\textsuperscript{3} of a higher frequency of apathy after lesions in the anterior choroidal artery territory, which involves the posterior limb of the internal capsule and the adjacent globus pallidus.

A wide spectrum of psychomotor disturbances has been described following lesions in the inner pallidum and the posterior limb of the internal capsule, ranging from motor neglect and psychic akinesia to akinetic mutism.\textsuperscript{28-30} The ansa lenticularis, which is the main output of the internal pallidum, occupies part of the posterior limb of the internal capsule.\textsuperscript{31,32} This pathway has a pallidomesencephalic projection ending in the pedunculopontine nucleus. This structure, localized within the mesencephalic locomotor region in cats and rodents, sends monosynaptic projections to motoneurons in the anterior horn and has a prominent role in goal-oriented locomotor behavior.\textsuperscript{33} Another pallidal projection also goes through the ansa lenticularis and reaches the pedunculopontine nucleus after a synapse in the substantia nigra pars reticulata.\textsuperscript{32} This pallidomesencephalic projection provides limbic innervation to both a somatic motor mechanism and the dopaminergic nigrostriatal system, and disruption of this circuit may underlie the bradyphrenia shown by apathetic patients. Thus, apathy might involve biogenic amine dysfunction and posterior limb lesions. Lesions of the ventral striatum could produce disruption of the ascending biogenic amine pathways and extend into the posterior limb, producing a disruption of the pallidomesencephalic projection. Perhaps this explains why major depression and apathy are associated. Other explanations might also be proposed, and this issue should be examined in further studies.

In conclusion, the present study has demonstrated that apathy is a frequent finding among elderly stroke patients with or without depression. Poststroke apathy is significantly associated with more severe cognitive and physical impairments, older age, and lesions in the posterior limb of the internal capsule. Future studies may examine the provocative issue of whether treatment of depression will improve apathy.

Acknowledgments

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References


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